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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,932	11/22/2005	Peter Kufer	DEBE:059US	8324

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EXAMINER	
BAUGHMAN, MOLLY E	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,932	KUFER ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *24-34* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Applicant's election without traverse of Group II, claims 19-21 and corresponding SEQ ID NO: 4, 14, and 35 in the reply filed on 3/23/2007 is acknowledged.

2. Claims 1-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/23/2007.

3. Applicant's addition of claims 22-34 in the reply filed on 3/23/2007 is acknowledged. The additional claims also add a total of 71 additional sequences and as such, the examiner has determined a further restriction is required for prosecution on the merits.

Election/ Restriction

This application contains claims directed to the following patentably distinct Restriction Subgroups of the claimed invention. After election of one of the Groups above, Applicant is required to also elect a restriction subgroup. This is not a species election. Applicant will be required to cancel non-elected subject matter upon indication of allowable subject matter.

Each of the nucleotide sequences comprise a patentably distinct subgroup. According to the Official Gazette (OG) of the Patent Office (Mar.27, 2007) (shortened):

> "The office has reconsidered the policy set forth in the 1996 Notice [i.e. up to ten, independent and distinct molecules described by the nucleotide sequence] in view of the changes in the complexity of applications filed, the types of inventions claimed and the state oft the prior art in this technology since that time. Because of these changes, the search and examination of up to ten molecules described by their nucleotide sequence often consumes a disproportionate amount of Office resources over that expended in 1996. Consequently, with this Notice the Office rescinds the partial waiver

> of 37 CFR 1.141 et seq. for restriction practice in national applications filed under 35 U.S.C. 111(a), and 37 CFR 1.475 et seq. for unity of invention determinations in both PCT international applications and the resulting national stage applications under 35 U.S.C. 371. This Notice is effective immediately and is applicable to all pending applications." As such, "claims to polynucleotide molecules will be considered for independence, relatedness, distinction, and burden as for claims to any other type of molecule."

As such, applicant is required under 35 U.S.C. 121 to elect a single disclosed Subgroup consisting of no more than a total of ten Sequence IDs selected from SEQ ID NO:1 through SEQ ID NO: 74 for prosecution on the merits to which the claims shall be restricted, corresponding to the original restriction requirement dated 2/27/2007. Since the reply filed on 3/23/2007 elected group II, comprising SEQ ID NO: 4, 14 and 35 (i.e. 3 sequences), applicant is required to elect seven (7) additional sequences, which would therefore elect a TOTAL of 10 sequences for prosecution on the merits.

Applicant is advised that a reply to this requirement must include an identification of the restriction subgroup that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Should applicant traverse on the ground that the Restriction Subgroups are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the Restriction Subgroups to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

4. During a telephone conversation with Steven Highlander on 5/8/2007 a provisional election was made without traverse to prosecute the invention of SEQ ID NO: 44, 49, 50, 59, 60, 71, and 72 for claims 24-34. Affirmation of this election must be made by applicant in replying to this Office action. SEQ ID NO: 1-3, 5-13, 15-34, 36-43, 45-48, 51-58, 61-70, and 73-74 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Currently claims 19-34 and the corresponding SEQ ID NOs: 4, 14, 35, 44, 49, 50, 59, 60, 71, and 72, are under examination

Claim Objections

7. Claims 24-26, 29-34 are objected to because of the following informalities: they contain subject matter which is to a non-elected invention, particularly, non-elected sequences. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 22-23, 28-32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 22-23, and 28 are confusing because it appears the claims are drawn to limitations which are intended uses of the at least one cDNA primer and as such, it is unclear how the claims further limit the claim from which they depend (i.e. claim 19 and 27). While claims 29-32 are not particularly confusing, they depend from claim 28, which is confusing.

b. Claim 34 is confusing because it is unclear how the claim is further limiting. Claim 33 is drawn to PCR primers of SEQ ID NO: 59 and 60 from Group C, and SEQ ID NO: 71 and 72 from Group D. Claim 34 recites the limitations PCR-primers of Group C and PCR-primers of Group D, where "for a first round of PCR-amplification" and "for a second round of PCR-amplification" are intended uses and therefore, it is unclear how the claim further limits the PCR primers of claim 33.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 19, 22-23 and 27-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Sninsky et al. (US 5,386,022).

Sninsky teaches a composition comprising at least one suitable cDNA primer (entire document, specifically, claims 1-2).

It is noted that use of the cDNA primer "for simultaneous reverse transcription of at least two different MAGE gene transcripts in a single cDNA-synthesis reaction" in claim 19 and "for reverse transcription of an appropriate calibrator mRNA, wherein reverse transcription of the appropriate calibrator mRNA is simultaneous with..." in claim 27 is an intended use of the cDNA primer and as such, bears no weight in the claim. Therefore, Sninsky meets the limitations of the claim by teaching a composition comprising at least one suitable cDNA-primer and further comprising a suitable cDNA primer. It is also noted that due to the indefiniteness of claims 22-23, and 28, as described above, it cannot be determined how the art differs from the instant claimed invention.

12. Claims 19, 22-23 and 27-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoon et al. (US 6,057,105).

Hoon et al. teach at least one cDNA primer and also teaches using the at least one cDNA primer for simultaneous reverse transcription of at least two different MAGE

transcripts in a single cDNA-synthesis reaction (i.e. Example XIII, SEQ ID NO: 1, 2, 23, 24 for detection of MAGE-1 and MAGE-3 in a single cDNA-synthesis reaction). Hoon also teaches amplifying as a control during each reaction, the β-actin gene (col.17, lines 32-40).

13. Claims 19, 22-23 and 27-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Kirken et al. (US 2006/0051324).

Kirken et al. teach at least one cDNA primer and also teaches using the at least one cDNA primer for simultaneous reverse transcription of at least two different MAGE transcripts in a single cDNA-synthesis reaction (i.e. Example 1, primers in Table 2 for detection of MAGE-A1, A3, A4, A6, A10, and A12 in a single cDNA-synthesis reaction). He also teaches cDNA primers used during the same reaction to amplify calibrator mRNA for GAPDH (page 11[0144], and Table 2).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 20-21, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirken et al. (US 2006/0051324), as applied to claims 19, 22-23, and 27-28 above.

The teachings of Kirken et al. are discussed above. Kirken teaches an anti-sense primer targeting the gene MAGE-A1 which comprises the entire sequence of SEQ ID NO:14 (a.k.a. Mg1_RT5a) plus an additional 3 nucleotides on the 5' side.

One of ordinary skill in the art would have been motivated to make a composition comprising at least one primer or oligonucleotide with the sequence of SEQ ID NO:14 because Kirken et al. teach a primer with the exact sequence as SEQ ID NO:14, plus an additional 3 nucleotides for use in an RT-PCR reaction detecting multiple MAGE genes. One of ordinary skill in the art would have expected the primer of Kirken et al. to have essentially the same functional capabilities of a primer or oligonucleotide which has the same sequence but is shortened by three nucleotides. The skilled artisan would have had a reasonable expectation of success in making a primer with the exact same sequence as the primer of Kirken et al. and shortening it by three nucleotides. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to make a composition comprising at least one primer or oligonucleotide with the sequence of SEQ ID NO:14.

17. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirken et al. (US 2006/0051324) as applied to claims 20-21, and 24 above, and further in view of Scanlan et al. (US 6,686,147) and Buck et al., "Design Strategies and Performance of Custom DNA Sequencing Primers," Biotechniques, Sept. 1999, Vol.27, No.3, pp. 528-536.

The teachings of Kirken et al. are discussed above. Although Kirken teaches using two primers, one of which with the exact sequence as SEQ ID NO:14 (Mg1_RT5a), plus an additional 3 nucleotides, and the second, a sense primer (MAGE-A1, Table 2), he does not specifically teach the second primer with the sequence of SEQ ID NO:4 (MgRT3a).

Scanlan et al. teach screening for cancer by the detection of tumor associated genes and encoded proteins, wherein exemplary tumor associated genes and encoded proteins include MAGE-A2, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-B2, MAGE-B3, MAGE-B4, MAGE-C1, and MAGE-C2 (col.15, lines 53-61). Scanlan disclose SEQ ID NO:18, which is MAGEA1 cDNA and has the Genbank accession number NM_004988 (col.10-11, lines 35-36, 34-67 - 1-2 and col. 77-78). Scanlan also disclose nucleic acid sequences (NA Group 3), which code for cancer associated antigen precursor and hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence of SEQ ID NO:18 (col.12, lines 56-60). Also disclosed are reverse transcription examples where gene-specific primers for MAGE-A1 and MAGE-A3 are used in a single reaction (col.36-

37 and Example 4, col.40-41). SEQ ID NO:18 comprises the instant cDNA primer sequences, SEQ ID NO:4 and 14, as well as the MAGE-A1 sense primer of Kirken (col.77-78).

The above described references do not specifically disclose the identical primer sequence of SEQ ID NO:4, used in the claimed invention and discloses a primer with the exact sequence as SEQ ID NO:14 (Mg1_RT5a), but with an additional 3 nucleotides.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the MAGE gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby

testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make a primer of SEQ ID NO: 4 and 14 because Scanlan et al. shows that the sequence of MAGE-A1 gene was known in the art (SEQ ID NO:18, Genbank Acc. NM_004988) and that it was conventional in the art to design gene-specific primers to the sequence for use in an RT-PCR reaction to detect cancer. Kirken et al. also describe a primer with the exact sequence as SEQ ID NO:14 (Mg1_RT5a), plus an additional 3 nucleotides, as well as a second primer, comparable to SEQ ID NO:4, which amplifies the same known MAGE sequence from which the primers were derived. Furthermore, Scanlan states that "amplification protocols such as polymerase chain reaction using primers which hybridize to the sequences presented [i.e. SEQ ID NO:18] also can be used for detection of the cancer associated antigen genes or expression thereof" (col.14, lines 4-8) and Buck et al. demonstrate the capability of multiple primers to equivalently amplify the same targeted region. Therefore, the skilled artisan would have had a reasonable expectation of success in making similar primers to those of Kirken and Scanlan et al., targeting the MAGE gene. It would have been obvious to one of ordinary skill in the art

at the time of the invention to make primers with a sequences of SEQ ID NO: 4 and 14, which detects a sequence of the MAGE gene.

18. Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al., as applied to claims 19, 22-23 and 27-28 above, and further in view of Gellerfors et al. (US 6,537,777) and Sagner et al. (US 6,691,041).

The teachings of Hoon et al. are discussed above. Although Hoon teaches primers for amplification of calibrator mRNA (i.e. the β-actin gene, col.17, lines 32-40), he does not discuss PCR primers to PBGD according to SEQ ID NO:44, 49, and 50.

Gellerfors et al. teaches various sequences of human porphobilinogen deaminase (PBGD), one of which comprises the instant SEQ ID NO:44, 49, and 50 (i.e. SEQ ID NO:10, col.7 and 73-74). Gellerfors et al. also teach primers (Iso379, 382, 375 and 376) designed to amplify the PBGD gene (col.11, 13 and Table 1).

One of ordinary skill in the art would have been motivated modify the diagnostic composition of Hoon et al. to include primers with sequences of SEQ ID NO: 44, 49, and 50, targeting the PBGD gene because Gellerfors et al. show that the PBGD gene was well-known in the art and demonstrate that it was conventional in the art to design primers for a PCR reaction targeting the same PBGD sequence comprising the instant primer sequences, SEQ ID NO: 44, 49, and 50. Furthermore, Sagner et al. state that there is a need for a more efficient and reliable quantification of nucleic acids during PCR reactions which are error-prone and demonstrate that the use of primers targeting a reference nucleic acid during amplification reactions of target DNA provides an

efficiency-corrected quantification of nucleic acids (col.1-2, and 6). In example 1, Sagner demonstrate using primers targeting the PBGD gene in parallel of the target gene (CK20) during amplification, and further include a probe which hybridizes to a sequence of the PBGD gene (SEQ ID NO:7) which has the exact same sequence as the instant SEQ ID NO:44, plus one nucleotide on the 5' end and two nucleotides on the 3' end (col.13 and 17). Therefore, the skilled artisan would have had a reasonable expectation of success in making similar primers to those of Gellerfors and Sagner et al., targeting the PBGD gene, and include it in the diagnostic composition of Hoon et al. for efficiency-corrected quantification of the target (MAGE) during PCR. It would have been obvious to one of ordinary skill in the art at the time of the invention to make a diagnostic composition and include primers with sequences consisting of SEQ ID NO: 44, 49, and 50, which detect a sequence of the PBGD gene.

19. Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirken et al., as applied to claims 19, 22-23 and 27-28 above, and further in view of Gellerfors et al. (US 6,537,777) and Sagner et al. (US 6,691,041).

The teachings of Kirken et al. are discussed above. Although Kirken teaches cDNA primers used during the same reaction to amplify calibrator mRNA (i.e. GAPDH (page 11[0144], and Table 2), he does not discuss PCR primers to PBGD according to SEQ ID NO:44, 49, and 50.

Gellerfors et al. teaches various sequences of human porphobilinogen deaminase (PBGD), one of which comprises the instant SEQ ID NO:44, 49, and 50 (i.e.

SEQ ID NO:10, col.7 and 73-74). Gellerfors et al. also teach primers (Iso379, 382, 375 and 376) designed to amplify the PBGD gene (col.11, 13 and Table 1).

One of ordinary skill in the art would have been motivated modify the diagnostic composition of Kirken et al. to include primers with sequences of SEQ ID NO: 44, 49, and 50, targeting the PBGD gene instead of GAPDH because Gellefors et al. show that the PBGD gene was well-known in the art and demonstrate that it was conventional in the art to design primers for a PCR reaction targeting the same PBGD sequence comprising the instant primer sequences, SEQ ID NO: 44, 49, and 50. Furthermore, Sagner et al. state that there is a need for a more efficient and reliable quantification of nucleic acids during PCR reactions which are error-prone and demonstrate that the use of primers targeting a reference nucleic acid during amplification reactions of target DNA provides an efficiency-corrected quantification of nucleic acids (col.1-2, and 6). In example 1, Sagner demonstrate using primers targeting the PBGD gene in parallel of the target gene (CK20) during amplification, and further include a probe which hybridizes to a sequence of the PBGD gene (SEQ ID NO:7) which has the exact same sequence as the instant SEQ ID NO:44, plus one nucleotide on the 5' end and two nucleotides on the 3' end (col.13 and 17). Therefore, the skilled artisan would have had a reasonable expectation of success in making similar primers to those of Gellefors and Sagner et al., targeting the PBGD gene, and include it in the diagnostic composition of Kirken et al., instead of GAPDH, for efficiency-corrected quantification of the target (MAGE) during PCR. It would have been obvious to one of ordinary skill in the art at the time of the invention to make a diagnostic composition and include primers with

sequences consisting of SEQ ID NO: 44, 49, and 50, which detect a sequence of the PBGD gene.

20. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoon et al., as applied to claims 19, 22-23 and 27-28 above, and further in view of Boon-Falleur et al. (US 6,221,593 B1) and Buck et al., "Design Strategies and Performance of Custom DNA Sequencing Primers," Biotechniques, Sept. 1999, Vol.27, No.3, pp. 528-536.

The teachings of Hoon et al. are discussed above. Although Hoon describes multiple PCR primers (i.e. Example XIII, SEQ ID NO: 1, 2, 23, 24 for detection of MAGE-1 and MAGE-3 in a single cDNA-synthesis reaction), he does not describe the primers with sequences of SEQ ID NO: 59, 60, 71, or 72 (MAGE-A10 primers in Group C, and MAGE-A10 primers in Group D).

Boon-Falleur et al. describe the sequence of the MAGE-10 gene, SEQ ID NO:3, which comprises the sequences of the instant primers of SEQ ID NO: 59, 60, 71, and 72. Boon-Falleur also describe designing PCR primers for use in a PCR reaction following reverse transcription in Example 11, which are nearby (nucleotides 264-283 and 726-748 of SEQ ID NO:3) to the instant primers of SEQ ID NO: 59, 60, 71, and 72 (nucleotides 178-197 (#59), 251-261 (#71), 382-363 (#72), 563-542 (#60) of SEQ ID NO:3) (Col. 11-14). Boon-Falleur states that the sequence of the invention can be used in various hybridization assays, such as PCR based assays, wherein the assays use oligonucleotide molecules which hybridize to MAGE-10 DNA or mRNA (col.11, lines 6-8, 14-15). Such molecules have complementary sequences that hybridrize to SEQ ID

NO:3 under stringent conditions, and preferably should include, at a minimum, nucleotides 164-574 of SEQ ID NO:3, where nucleotides 164-185 (comprising nucleotides of the instant primer of SEQ ID NO:59) and 553-574 of SEQ ID NO:3 are especially useful as probes and/or primers (col.10, lines 60-67 - col.11, lines 1).

The above described references do not specifically disclose the identical primer sequences of SEQ ID NOs:59, 60, 71 and 72, respectively, in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the MAGE-10 gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods

of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

One of ordinary skill in the art would have been motivated modify the diagnostic composition of Hoon et al. to include primers with sequences of SEQ ID NO: 59, 60, 71, and 72 because Boon-Falleur et al. show that the MAGE-10 gene of was well-known in the art and demonstrate that it was conventional in the art to design primers for a PCR reaction targeting the same region of reverse transcribed MAGE-10 cDNA as SEQ ID NO: 59, 60, 71, and 72. Boon-Falleur also states that, "the art is familiar with the design of such molecules. For example, it is well known that when RT-PCR is carried out, primers are generally 18-23 nucleotides long with the 6-8 nucleotides at the 3' end being essentially 100% complementary to the target" (col.11, lines 21-25) and also state that sequences that hybridize to nucleotides 164-574 of SEQ ID NO:3 (including the instant sequences of SEQ ID NO: 59, 60, 71 and 72) are particularly useful for the detection of cancer. Furthermore, Buck et al. demonstrate the capability of multiple primers to equivalently amplify the same targeted region. Therefore, the skilled artisan would have had a reasonable expectation of success in making a similar primer to those of Boon-Falleur et al., targeting the MAGE-10 gene, and include it in the diagnostic composition of Hoon et al. It would have been obvious to one of ordinary skill in the art

at the time of the invention to make a diagnostic composition and include primers with sequences consisting of SEQ ID NO: 59, 60, 71, and 72, which detect a sequence of the MAGE-10 gene.

21. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirken et al., as applied to claims 19, 22-23 and 27-28 above, and further in view of Boon-Falleur et al. (US 6,221,593 B1) and Buck et al., "Design Strategies and Performance of Custom DNA Sequencing Primers," Biotechniques, Sept. 1999, Vol.27, No.3, pp. 528-536.

The teachings of Kirken et al. are discussed above. Although Kirken describes multiple PCR primers (Table 2, page 11), he does not describe the primers with sequences of SEQ ID NO:59, 60, 71, or 72 (MAGE-A10 primers in Group C, and MAGE-A10 primers in Group D).

Boon-Falleur et al. describe the sequence of the MAGE-10 gene, SEQ ID NO:3, which comprises the sequences of the instant primers of SEQ ID NO: 59, 60, 71, and 72. Boon-Falleur also describe designing PCR primers for use in a PCR reaction following reverse transcription in Example 11, which are nearby (nucleotides 264-283 and 726-748 of SEQ ID NO:3) to the instant primers of SEQ ID NO: 59, 60, 71, and 72 (nucleotides 178-197 (#59), 251-261 (#71), 382-363 (#72), 563-542 (#60) of SEQ ID NO:3) (Col. 11-14). Boon-Falleur states that the sequence of the invention can be used in various hybridization assays, such as PCR based assays, wherein the assays use oligonucleotide molecules which hybridize to MAGE-10 DNA or mRNA (col.11, lines 6-

8, 14-15). Such molecules have complementary sequences that hybridrize to SEQ ID NO:3 under stringent conditions, and preferably should include, at a minimum, nucleotides 164-574 of SEQ ID NO:3, where nucleotides 164-185 (comprising nucleotides of the instant primer of SEQ ID NO:59) and 553-574 of SEQ ID NO:3 are especially useful as probes and/or primers (col.10, lines 60-67 - col.11, lines 1).

The above described references do not specifically disclose the identical primer sequences of SEQ ID NOs:59, 60, 71 and 72, respectively, in the claimed invention.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the MAGE-10 gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby

testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

One of ordinary skill in the art would have been motivated modify the diagnostic composition of Kirken et al. to include primers with sequences of SEQ ID NO: 59, 60, 71, and 72 because Boon-Falleur et al. show that the MAGE-10 gene of was well-known in the art and demonstrate that it was conventional in the art to design primers for a PCR reaction targeting the same region of reverse transcribed MAGE-10 cDNA as SEQ ID NO: 59, 60, 71, and 72. Boon-Falleur also states that, "the art is familiar with the design of such molecules. For example, it is well known that when RT-PCR is carried out, primers are generally 18-23 nucleotides long with the 6-8 nucleotides at the 3' end being essentially 100% complementary to the target" (col.11, lines 21-25) and also state that sequences that hybridize to nucleotides 164-574 of SEQ ID NO:3 (including the instant sequences of SEQ ID NO: 59, 60, 71 and 72) are particularly useful for the detection of cancer. Furthermore, Buck et al. demonstrate the capability of multiple primers to equivalently amplify the same targeted region. Therefore, the skilled artisan would have had a reasonable expectation of success in making a similar primer to those of Boon-Falleur et al., targeting the MAGE-10 gene, and include it in the

diagnostic composition of Kirken et al. It would have been obvious to one of ordinary skill in the art at the time of the invention to make a diagnostic composition and include primers with sequences consisting of SEQ ID NO: 59, 60, 71, and 72, which detect a sequence of the MAGE-10 gene.

Summary

22. Claims 29-30 are free of the prior art, but are rejected and objected to for other reasons. No prior art has been found teaching or suggesting the sequence comprising or consisting of primer PBGD_RT15b (SEQ ID NO: 35) in claim 29.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Molly E Baughman
Examiner
Art Unit 1637

MEB 5/24/07

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

5/29/07